The HELPER programme: HEalthy Living and Prevention of Early Relapse – three exploratory randomised controlled trials of phase-specific interventions in first-episode psychosis

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Scientific summary

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Background

Schizophrenia represents a substantial cost to the NHS and society because it is common (lifetime prevalence around 0.5–1%); it begins in adolescence or early adulthood and often causes lifelong impairment. The first 3 years are a 'critical period' in which the course of the illness is determined. Hence, under the NHS Plan, specialist early intervention in psychosis services were established to care for people who develop psychosis between the ages of 14 and 35 years for the first 3 years of their illness. However, there has been a lack of evidence-based treatments specifically designed for the early years. This is important because emerging evidence has shown that in the critical period it is vital to avoid relapse and prevent deterioration in physical health, as both can drastically reduce the chances of a full recovery.

It is important to avoid relapse after the first episode because with each successive relapse the illness becomes more difficult to treat; the number of individuals who achieve a full recovery declines; and the level of residual disability mounts. Those who relapse are more likely to have poor outcomes such as treatment resistance, suicide and causing harm to others. Studies from the UK and abroad have shown that our success in preventing relapse is poor. Although 85% of people who develop psychosis recover fully from the first episode, 48–51% may relapse within 18 months, even within early-psychosis teams. Over a 5-year follow-up as many as 80% may relapse.

One way to avoid relapse is to make psychological treatments more effective. An evaluation of cognitive remediation (CR) in combination with cognitive–behavioural therapy (CBT) was included in this study, as CR targets neuropsychological deficits that predispose to poor insight and hamper participation with therapy. CR was evaluated in people on the waiting list for cognitive therapy to see whether or not prior receipt of CR improved their meta-cognition and insight, enhanced their subsequent engagement in cognitive therapy and ultimately reduced relapse.

Antipsychotic medication is a key way of preventing relapse but unfortunately it can contribute to poor health. Physical inactivity and poor diet are more common in people with schizophrenia than in the general population and antipsychotic medication amplifies the effect of these risk factors. In the UK in the 1990s the standardised mortality ratio (SMR) for death from natural causes was 232 [95% confidence interval (CI) 172 to 600] for people with schizophrenia. The SMR was 468 for avoidable causes, 187 for cardiovascular disease, 534 for cerebrovascular disease and 996 for diabetes mellitus. This high level of mortality is a result of lack of physical activity, smoking and reduced access to preventative treatments. These SMRs have since increased, with much of the increase attributable to deaths from natural causes, especially circulatory disease and respiratory disease. As Saha *et al.* state, 'in light of the potential for second-generation antipsychotic medications to further adversely influence mortality rates . . . optimising the general health of people with schizophrenia warrants urgent attention' (Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 2007;**64**:1123–31). Intervention in the critical period is the key to preventing this excess mortality because this is when (1) most antipsychotic medication-induced weight gain occurs; (2) diabetes mellitus develops; and (3) unhealthy behaviours such as inactivity and substance misuse become deeply ingrained. Our systematic reviews of treatments in early-psychosis and healthy-living interventions in schizophrenia have shown that there are no established phase-specific interventions for preventing relapse or deterioration in health, and we therefore developed a healthy-living intervention aimed at reducing weight. We expected that if people felt healthier they might have lower rates of relapse.

We also targeted substance use, in particular cannabis use, as it predicts relapse in first-episode patients and because rates of substance use in first-episode psychosis are high.

Objectives

The overarching aim of the HEalthy Living and Prevention of Early Relapse (HELPER) programme was to develop three linked phase-specific interventions to prevent relapse of psychosis and/or deterioration in physical health in people who have experienced a first episode of psychosis. The interventions, linked by a common theoretical framework (the self-regulatory model of illness management), were designed for optimum delivery by the national network of early-intervention service teams. The main objectives of the programme were to:

1. evaluate CR to improve meta-cognition and insight and enhance engagement in cognitive therapy [the IMproving PArticipation in Cognitive Therapy (IMPACT) trial]
2. develop and evaluate a healthy-living intervention to control weight in people taking antipsychotic medication after a first episode of psychosis [the INTERvention to Encourage ACTivity, Improve Diet, and Reduce Weight Gain (InterACT trial)]
3. optimise and evaluate motivational interviewing (MI) and CBT for substance misuse [the Asking about Substance use and Psychosis – Ideas, Reactions and Experiences (ASPIRE) and Rethinking Choices After Psychosis (ReCAP) trials]
4. identify any trends towards lower relapse rates within and across trials (IMPACT, InterACT and ReCAP trials).

The trials were exploratory in nature and designed to make the case (or otherwise) for larger definitive trials with relapse as a primary outcome measure. However, as small exploratory trials do not have sufficient power to detect clinically significant reductions in relapse, each trial was focused on a relevant primary outcome for which there was sufficient power to detect a clinically significant difference. In all three trials relapse was a secondary outcome, with the aim of detecting trends towards lower relapse rates in the presence of effective interventions or a general trend across all three studies towards lower relapse rates.

Methods

The three interventions included in the programme are complex and were evaluated in line with the Medical Research Council (MRC) framework for the development and evaluation of complex interventions. The two interventions that were optimised for the programme were informed by preliminary qualitative work using grounded theory and framework analysis to ensure that the illness models of the intended participants were taken into account in the adaptation (as specified by the self-regulatory model). The three trials evaluating the interventions were all methodologically robust single-blind randomised controlled trials: two exploratory and one pragmatic. The IMPACT trial involved 61 patients who were on the waiting list for cognitive therapy, with 31 randomised to receive CR and 30 randomised to receive social contact. In the InterACT trial, 105 participants consented to take part: 54 were randomised to the healthy-living group and 51 were randomised to the treatment-as-usual (TAU) group. In the ReCAP trial 110 participants were randomised to brief therapy ($n = 38$), longer duration therapy ($n = 37$) or TAU ($n = 35$).

Results

Engagement and retention rates in all three trials were good, indicating that the interventions were feasible to deliver and acceptable to participants. Our hypotheses concerning the impact of the interventions on outcome were partially supported. In the IMPACT trial, CR was not associated with significantly lower Psychotic Symptom Rating Scales (PSYRATS) scores over the period of study ($p = 0.39$) but was associated with better insight ($p = 0.02$). CR improved the efficiency of CBT ($p = 0.011$); after CR, participants made the same amount of progress in half the number of CBT sessions. Global cognition did not improve significantly more after CR ($p = 0.20$) but executive function did (Wisconsin Card Sort Task; $p = 0.012$). In the InterACT trial the healthy-living intervention was associated with a small reduction in body mass index (BMI) in the intervention group but not in the TAU group, but the effect size was

small (0.11) and the difference not statistically significant ($p = 0.44$). There was evidence to suggest that the intervention may be more effective in participants taking olanzapine and clozapine (effect size 0.55 for weight loss, 0.54 for BMI reduction); although, again, these differences were not statistically significant ($p = 0.19$ and 0.20 respectively). Health and social care costs were lower in the TAU group but the difference was not statistically significant ($p = 0.69$) and relapse rates were similar. However, full cost data were not available for all participants who completed follow-up and further analysis is planned. In the ReCAP trial, integrated motivational interviewing and cognitive–behavioural therapy (MiCBT) was accepted by the majority of people to whom it was offered (80%), indicating that the intervention was acceptable to participants. The median number of therapy sessions attended in both of the therapy arms was similar, indicating that a brief form of the intervention may be more acceptable than a longer form. There was no difference in relapse rates between the three arms.

Conclusions

Early-intervention services provided a good setting to conduct trials of phase-specific interventions, and good rates of recruitment and retention were achieved across all three trials.

The IMPACT trial showed that CR delivered by relatively unskilled workers can improve the efficiency of subsequent CBT, enabling participants and therapists to achieve the same amount of progress in therapy in approximately half the number of sessions. A substantial increase in the efficiency of CBT implies that the same number of CBT therapists could treat many more patients.

The InterACT trial showed that we were able to train support, time and recovery workers to deliver a healthy-living intervention but that the effect of the intervention on weight reduction or controlling weight gain was small and not statistically significant. The effect of the intervention was larger in the subgroup taking olanzapine and clozapine, suggesting that future work should focus attention on this subgroup of service users.

The ReCAP trial showed that the MiCBT intervention was acceptable to young cannabis users in early psychosis, but it is not yet known whether or not MiCBT improved outcome in terms of reducing cannabis use or improving clinical outcome. The results, when available, will be a significant addition to the evidence base and will be of considerable interest to academics and clinicians in the field.

Recommendations for future research

In order of priority:

1. The IMPACT trial may have shown that CR had a positive impact on the efficiency of CBT. We therefore recommend that a definitive trial of CR-aided CBT should be conducted with improvement in the efficiency of CBT as the primary outcome measure.
2. The InterACT trial showed that a healthy-living intervention might possibly work better for people who are taking olanzapine or clozapine. Further work should, therefore, be carried out to improve the effectiveness of the healthy-living intervention, particularly with a focus on those who are taking olanzapine or clozapine.
3. We found that early-intervention services provided a good setting for carrying out research because they support retention and recruitment and there is strong engagement from service users and staff. Consideration should be given to setting up a national programme of phase-specific research within early-intervention services.

Trial registration

The IMPACT trial is registered as ISRCTN17160673, the InterACT trial is registered as ISRCTN22581937 and the ReCAP trial is registered as ISRCTN88275061.

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